## REMARKS

Reconsideration of the application and entry of the amendments is requested. The following documents accompany this response:

1. Transmittal Letter
2. Extension of Time and Fee
3. Microorganism Declaration
4. Sequence Listing
5. Statement under 37 C.F.R. §1.825(a)
6. Statement under 37 C.F.R. §1.825(b)
7. Computer Readable Form (CRF)
8. Claims - Appendix A

Claims 2-5, 10-12 and 30 have been deleted. Claims 1 and 26-29 remain in the application. A substitute Sequence Listing accompanies this Amendment. It is understood that this Sequence Listing lists all of the sequences in the application, and the sequences are referenced by the sequence identifiers in the application. It is understood that the application now complies with the requirements of 37 C.F.R. §§1.821 through 1.825.

### Rejections Under 35 U.S.C. §112

Claim 3 is rejected as being indefinite for failing to particularly point out and claim the subject matter which Applicants regard as the invention. Without considering the merits of the rejection, claims 3 has been deleted thus obviating the rejection based thereon.

The specification is objected to and claim 3 rejected for failing to provide an enabling disclosure because the specification does not provide a repeatable method for obtaining ATCC #75010 and it does not appear to be readily available material. Submitted herewith is a Declaration by the undersigned attorney stating that the deposit has been made under the terms

of the Budapest Treaty and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent. Furthermore, the full address of the ATCC has been added to the specification. It is therefore understood that the deposit requirements under 37 C.F.R. §1.808 have been satisfied.

Claims 1-5, 10-12 and 26-30 are rejected as the disclosure is enabling only for claims limited to wherein a disulfide-linked dimer is formed wherein each of the two subunits comprises at least portions 4-142 of SEQ ID NO:14. Claims 2-5, 10-12 and 30 have been deleted. Claim 1 has been amended to recite the sequences of SEQ ID NOS:1-3 and further characterize the protein as a disulfide linked dimer and by molecular weight and activity. The claimed invention therefore indicates amino acid sequences necessary for activity, molecular weight and the requirement of conformation as a disulfide linked dimer wherein each subunit contains the sequences recited in the claim. It is understood that the claims as amended are commensurate with the enablement of the specification.

**Rejections Under 35 U.S.C. §102**

Claims 1-5, 10-12 and 30 are rejected under 35 U.S.C. §102(*e*) as being anticipated by US 5,266,683 ('683). Claims 26-29 are rejected under 35 U.S.C. §102(e) as anticipated by US 5,354,556 ('557).

As set forth above, claims 2-5, 10-12 and 30 have been deleted. Remaining claims 1 and 26-29 are based on disclosure in application USSN 07/525,357 filed May 16, 1990 for which applicants have claimed the benefit of priority in the present application. Although the '683 and

'557 patents may claim priority dates to April 8, 1988, it is understood that the hOP2 disclosure of '683 and '557 upon which the Examiner relies is not found in the applications having earlier priority dates claimed in '683 and '557. Rather, it is Applicants understanding that the hOP2 disclosure was set forth in USSN 599,543 filed October 18, 1990. (See document "BM" WO92/07073 listed on page 2 of the Information Disclosure Statement). It is therefore submitted that the claimed invention is not anticipated by the '683 or '557 patents.

**Rejections Under 35 U.S.C. §103**

Claims 1, 2 and 26-29 are rejected as being unpatentable over US 5,011,691 in view of Zoller et al. The '691 patent is cited for disclosure of bone morphogenic proteins and amino acid sequence alignment of various homologous osteogenic proteins showing what regions are conserved. The Examiner contends that it would have been obvious to one skilled in the art to substitute Lys for Gln in the OP1 sequence in Figure 18-1 having the same sequence in Figure 18-3 as "c" in claim 1 using the techniques of Zoller et al. or other conventional techniques to obtain a mutein having the osteogenic activity of OP1. It is further contended that it would have been obvious to use such muteins in compositions.

Claim 2 has been deleted and claims 1 and 26-29 have been amended. The claims as amended characterize the BMP-8 protein by each of the sequences of parts (i)-(iii). Furthermore the BMP proteins belong to a supergene family based on homologies. The OP-1 sequence of '691 is homologous with BMP-7, a member of this family of proteins. The '691 patent does not, however, teach the presently claimed BMP-8 protein, nor in fact that a BMP-8 protein

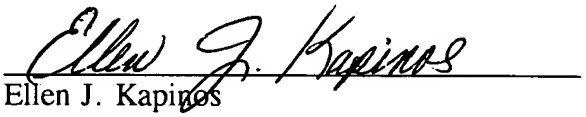
exists. It is therefore submitted that the claimed invention is not obvious over the '691 patent in view of Zoller et al.

## CONCLUSION

In view of the foregoing remarks and amendments, Applicants respectfully request reconsideration and withdrawal of the rejections of record and issuance of the claims. Should the Examiner believe that a telephonic interview would assist in clarifying any remaining issues, or to otherwise expedite prosecution, Applicants respectfully invite the Examiner to call the undersigned attorney at the telephone number provided below.

If any fee is due in regard to this paper, Applicants hereby authorize payment of such fee from Deposit Account No. 07-1060.

Respectfully submitted,



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## APPENDIX A

1. A purified BMP-8 protein characterized by:

(a) the following sequences:

i) Arg-His-Glu-Leu-Tyr-Val-Ser-Phe-Gln-Asp-Leu-Gly-Trp-Leu-Asp-Trp-Val-Ile-Ala-Pro-Gln-Gly-Tyr (SEQ ID NO:1);

ii) Leu-Ser-Ala-Thr-Ser-Val-Leu-Tyr-Tyr-Asp-Ser-Ser-Asn-Asn-Val-Ile-Leu-Arg (SEQ ID NO: 2); and

iii) Ala-Cys-Cys-Ala-Pro-Thr-Lys (SEQ ID NO: 3);

(b) a molecular weight of 28,000 - 38,000 daltons as determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis; and

(c) a molecular weight of 14,000 - 20,000 daltons under reducing conditions as determined by sodium dodecyl sulfate polyacrylamide gel electrophoresis said protein being a disulfide linked dimer wherein each of the subunits contains the sequences set forth in part (a) and said protein having the ability to induce the formation of cartilage and/or bone.

26. A pharmaceutical formulation for bone and/or cartilage formation comprising an effective amount of a BMP-8 protein of claim 1 in a pharmaceutically acceptable vehicle.

27. A composition of claim 26 further comprising a matrix for supporting said composition and providing a surface for bone and/or cartilage formation.

28. The composition of claim 27 wherein said matrix comprises a material selected from the group consisting of hydroxyapatite, collagen, polylactic acid and tricalcium phosphate.

29. A pharmaceutical composition for wound healing and tissue repair said composition comprising an effective amount of a BMP-8 protein of claim 1 in a pharmaceutically acceptable vehicle.